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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 09/978,191
Filing Date: October 15, 2001
Appellant(s): GODDARD ET AL.

Christopher De Vry
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 18 November 2008 appealing from the Office action mailed 25 March 2008.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The Examiner is aware of one related appeals, interferences, or judicial proceedings which may directly affect or have a bearing on the Board's decision in the pending appeal directed to the polypeptide referred to as PRO213-1. The application is 09/904,766 and is related in that the application is by the same assignee and shares several inventors with the instant application. It was recently appealed on virtually identical rejections and evidence. The Board affirmed the Examiner's rejections in '766.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The Appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Konopka et al. "Variable Expression of the Translocated c-abl Oncogene in Philadelphia-Chromosome-Positive B-Lymphoid Cell Lines from Chronic Myelogenous Leukemia Patients" Proc. Natl. Acad. Sci. USA, vol83 (1986), pp. 4049-4052.

Pennica et al. "WISP Genes Are Members of the Connective Tissue Growth Factor Family That Are Up-Regulated in WNT-1-Transformed Cells and Aberrantly Expressed in Human Colon Tumors" " Proc. Natl. Acad. Sci. USA, vol95 (1998), pp. 14717-14722.

Godbout et al. "Overexpression of a DEAD Box Protein (DDX1) in Neuroblastoma and Retinoblastoma Cell Lines" J. Biol. Chem. vol273, no33 (14 August 1998), pp. 21161-21168.

Li et al. "Identification of Putative Oncogenes in Lung Adenocarcinoma by a Comprehensive Functional Genomic Approach" Oncogene, vol25 (2006), pp. 2628-2635.

Sen, S. "Aneuploidy and Cancer" Curr. Opin. Oncol., vo112 (2000), pp. 82-88.

Hittleman, W.N. "Genetic Instability in Epithelium Tissues at Risk for Cancer" Ann. NY Acad. Sci., vol:952 (2001), pp. 1-12.

Hanna, J.S. and Mornin, D. "HER-2/neu Breast Cancer Predictive Testing" Pathology Associates Medical Laboratories (19999), pp. 1-2.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63 and 69-70 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

The claims are directed to isolated polypeptides comprising the amino acid sequence of amino acid residues 35-273 of SEQ ID NO: 506. Claims are also presented to chimeric proteins comprising the aforementioned polypeptide. The specification discloses the polypeptide of SEQ ID NO: 506, also known as PRO213-1. Appellant has gone on record as relying upon the gene amplification assay as providing

utility and enablement for the claimed polypeptides. See Appeal Brief (received 18 November 2008), p. 4, beginning of arguments.

At pages 331-345 of the specification, Example 114 discloses a gene amplification assay in which genomic DNA encoding PRO213-1 had a ΔCt value of at least 1.0 for 34 out of 37 lung tumor samples (and 16 out of 19 lung tumors) and eleven out of 17 colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 114 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer. ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 341-345 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

There are problems with the data provided in this example. The art recognizes that lung epithelium can be aneuploid without the presence of cancer. Specifically Sen (2000, Curr. Opin. Oncol. 12:82-88) teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification

of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The gene amplification assay in the instant specification does not provide a comparison between the lung/colon tumor samples and normal lung/colon tissue and does not correct for aneuploidy. Thus, it is not clear that PRO213-1 is amplified in cancerous lung epithelium more than in damaged (non cancerous) lung epithelium (or in colon cancer versus normal colon tissue). One skilled in the art would not conclude that PRO213-1 is a diagnostic probe for lung or colon cancer unless it is clear that PRO213-1 is amplified to a clearly greater extent in true lung/colon tumor tissue relative to non-cancerous lung/colon tissue.

Even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the claimed PRO213-1 *polypeptides*. In order for PRO213-1 polypeptides to be overexpressed in tumors, amplified genomic DAN would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO213-1 mRNA or PRO213-1 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA

> amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." (p. 14722, second paragraph of left column)

Additional details are provided in the section entitled, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors" on pp. 14720-14721. Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that, "Protein expression is not related to amplification of the *abl* gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph1 template" (see abstract). Hanna and Mornin (1999, Pathology Associates Medical Laboratories) also supports the instant rejections. Hanna and Mornin provide another important example of a lack of correlation between gene amplification and mRNA/polypeptide overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus, Hanna and Mornin provide evidence that the level of polypeptide expression must be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO213-1 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed polypeptides is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

The *general* concept of gene amplification's lack of correlation with mRNA/polypeptide overexpression in cancer tissue is addressed by Godbout et al. (J. Biol. Chem 273(33):21161, 1998) who teach a general lack of correlation between gene amplification and mRNA/polypeptide overexpression. The abstract of Godbout et al. teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified***." (emphasis added). The polypeptide encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably

incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO213-1 confers any growth advantage to a cell, and thus it cannot be presumed that the PRO213-1 polypeptide is overexpressed because the genomic DNA including the gene being studied is amplified.

An additional reference that provides evidence that gene amplification does not necessarily lead to increased transcript is Li et al. (Oncogene, Vol. 25, pages 2628-2635, 2006). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, paragraph beginning at the bottom of col. 1, Li et al. state:

> Although the main focus of this study was to specifically identify putative oncogenes, it should be noted that 90.7% of the genes showing high protein expression did not show corresponding increases in both DNA copy number and transcript, a finding consistent with that of others that transcriptional, translational, and post-translational regulatory mechanisms can greatly influence the abundance of protein in lung tumorigenesis (Chen *et al.*, 2002).... **In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels**, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*. (emphasis added)

Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that it is more likely than not that ***gene amplification does NOT correlate with increased protein levels***, absent evidence that the polypeptide has biological relevance in cancer. There is no such evidence for PRO213-1.

While the Examiner has the resources to cite only a handful of references showing the unpredictability of a correlation between genomic DNA and protein levels,

these references stand to show that one cannot make assumptions about the use of PRO213-1 polypeptide in view of the methods used and information provided in the instant specification. Therefore, data pertaining to PRO213-1 genomic DNA do not indicate anything significant regarding the claimed PRO213-1 polypeptides. The data do not support the specification's assertion that PRO213-1 polypeptides can be used as cancer diagnostic agents. Significant further research would have been required of the skilled artisan to reasonably confirm that the PRO213-1 polypeptide is overexpressed in any cancer to the extent that the polypeptide could be used as a cancer diagnostic agent, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO213-1 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO213-1 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides and antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Sen, Godbout et al., and Li et al.), the rejection is properly maintained.

Claims 63 and 69-70 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

**(10) Response to Argument**

**ISSUE 1: 101/112, First Paragraph rejections of claims 63 and 69-70 based on the results of the gene amplification assay**

At pages 4-5 and 10 of Appellants' brief, it is argued that the data in Example 114 describes results of a gene amplification assay. Appellants characterize the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Appellants report that the gene encoding PRO213-1 was significantly amplified (2.04-fold to 46.9-fold) in 16/19 lung tumor samples and (2.27-fold to 13.8-fold) in 11/17 colon tumor samples. This has been fully considered but is not found to be persuasive. First, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (page 228 of the specification). The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy (see, *e.g.,* Sen et al., J. Biol. Chem.

273(33):21161-21168, 1998, and Hittelman et al., Ann N.Y. Acad, Sci 952:1-12, 2001). Given these details, one skilled in the art would not conclude that the gene encoding PRO213-1 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA or polypeptide levels (see Pennica et al., Konopka et al., Godbout et al. and Li et al.).

Appellant argues (page 4, page 10, page 13-14, and page 19 through page 25) that ample evidence has been provided to show that, in general, if a gene is amplified in cancer, it is more likely than not that the corresponding mRNA and encoded polypeptide are also expressed at an elevated level. Appellant refers to Orntoft et al., Hyman et al. and Pollack et al. as teaching that, in general, gene amplification increases mRNA expression. Additionally, it is argued that Hyman et al. and Pollack et al. did not use traditional CGH analysis to identify amplified genes, while they did analyzed copy number on a gene-by-gene basis. These arguments have been fully considered but are not found to be persuasive. Orntoft et al. looked at increased DNA content over large regions of chromosomes and compared that to mRNA and polypeptide levels from the chromosomal region (see for example, page 44, last paragraph of col. 1). Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of

individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with clusters of chromosomal material containing strong gains, but it is not known whether PRO213-1 is in a gene cluster in a region of a chromosome that is highly amplified, which is pertinent because Orntoft et al. only provide information about genes in clusters (large chromosomal regions). The data of Orntoft et al. are not from looking at a 1:1 correspondence of genomic DNA and the mRNA which is transcribed from it. If PRO213-1 is not part of a cluster showing strong gains, then the findings of Orntoft et al. are not applicable. Because no such information was disclosed for PRO213-1, Orntoft et al. does not support Appellant's position. Ornoft et al. go on to say that detection was very limited.

While Hyman et al. and Pollack et al. combined CGH with microarray analysis, the results do not support a conclusion that the skilled artisan would reasonably expect amplified genomic DNA to correspond with overexpression of encoded protein. Hyman et al. used CGH in combination with cDNA microarray analysis. Less than half (44%) of *highly* amplified genes showed mRNA overexpression, and 10.5% of highly overexpressed transcripts had amplified genes (p. 6242, col. 1, third full paragraph). Thus, even at the level of high amplification and high overexpression, the two do not usually correlate. Polypeptide levels were not investigated. Further, Hyman et al. state that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributed to gene amplification (col. 1, middle, p. 6244). This proportion was about 2% of the total. The Examiner maintains that 2% does not provide

a reasonably expectation that the amplification of PRO213-1 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, the references supports the basis of the rejections that it is more likely than not that gene amplification fails to correlate with increased mRNA/polypeptide levels. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. concentrated on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Pollack et al. also noted contradictory results found by another research group, Platzer et al., who found a poor correlation between DNA amplification and overexpression (p. 12967, col. 2, 7 lines from bottom). Pollack et al. noted that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability, particularly when gene amplification of the instant PRO213-1 gene has been identified in lung and colon cancer instead of breast tumors.

Appellant argues (page 5 and page 13) that even if there were no correlation between gene amplification and mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer still has a patentable utility in that it yields more accurate tumor classification and provides significant information for cancer diagnosis and treatment, relying upon the declaration by Dr. Ashkenazi (submitted 10/04/04) and the "real world" example of breast cancer marker HER-2/neu of Hanna et al. reference. Appellant asserts that the Examiner has misread Hanna et al., who state gene

amplification and polypeptide expression are well correlated, with only a subset of tumors showing disagreement between the two measurements. Finally, Appellant concludes that there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PRO213-1 conveys utility to the claimed PRO213-1 polypeptides. These arguments have been fully considered but are not found to be persuasive. While it may be true that lack of overexpression of a gene product may also provide useful information in tumor categorization, the specification does not disclose such further testing of PRO213-1 gene product expression levels to facilitate categorization. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products based on the claimed invention are not in "currently available" form. Furthermore, the specification provides no assertion that the claimed PRO213-1 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO213-1. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial. Finally, Hanna et al. supports the rejection in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level of polypeptide expression must be tested empirically. Hanna et al. say these tests are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (col. 2, third full paragraph). The protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated

in the same paragraph that "In general, FISH [gene] and IHC[protein] results correlate well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." This teaches away from using gene amplification in cancer diagnosis or treatment. The identification of subsets of tumors without correlation affirms the unpredictability of the findings. Therefore, the issues of HER-2 cannot be generalized to any gene expressed in a tumor. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments to reasonably confirm the real world context of the asserted utility. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Again, because Hanna et al. studied breast cancer, the warning by Pollack et al. discussed in the preceding paragraph relating to the disparity in correlation of gene amplification and expression in breast compared to colon tumors is significant.

Appellant argues (page 7) "that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use." This statement relates to the Court's decision in *Nelson v. Bowler.* In that decision, the CCPA says that specific therapeutic use of a compound is not necessary if there are tests which evidence pharmacological activity of a compound. However, in this instance, pharmacological activity is not the same as gene amplification. In *Nelson,* the court held that the compound of which utility was in question, was shown to have a specific pharmacological activity measured by

dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (885). "Here, however, a correlation between test results and pharmacological activities has been established." (886) Unlike in *Nelson*, the instant application does not have a showing of practical utility. There are no test results to correlate the presence of PRO213-1 polypeptide with a diagnostic for lung or colon cancer. It is maintained that the instant application has not established the use of a polypeptide of SEQ ID NO:506 and utility as a cancer diagnostic. A finding of amplification of the genomic nucleic acid of SEQ ID NO:505 cannot be assumed to correlate to the higher expression of the encoded polypeptide in the same tissues.

On page 8, Appellant also cites *Cross v. Iizuka* (Fed. Cir. 1985), arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo*. The argument has been fully considered, but is not persuasive. At issue is **not** whether *in vitro* amplification data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is whether genomic DNA levels correlated with encoded protein levels.

Beginning on the bottom page 9 to page 10, Appellant asserts that patentable utility for the PRO213-1 polypeptides is based upon the gene amplification data for the gene encoding the PRO213-1 polypeptide. Appellants concludes that one skilled in the art would consider the 2.04-fold to 46.9-fold amplification of the gene encoding PRO213-1 in 19 lung tumors and lung cancer cell lines and 2.27-fold to 13.8-fold in 16 colon tumors and colon cancer cell lines is significant and credible. This has been fully

considered but is not found to be persuasive. Credibility has never been questioned. However, the significance can be questioned because the control used was not a matched non-tumor lung or colon sample, respectively, but rather was a pooled DNA sample from blood of healthy subjects. As discussed above, the art uses matched tissue samples. Pennica et al., Konopka et al., Sen et al., Hittelman et al., Godbout et al. and Li et al. speak to the strength of the opposing evidence as discussed in the rejections and response above and no evidence has been provided to indicate that an approximately 2-fold amplification of genomic DNA is predictive of protein expression levels in tumors. Pennica et al. was found to support the rejection, as discussed above. Finally, there is nothing in Example 114 that suggests that the encoded proteins thereof are found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides not genes, the data presented in Example 114 is not sufficient to establish a specific and substantial utility for the encoded and claimed protein.

At pages 10-11 of the Brief, Appellant reviews the gene amplification data disclosed in the specification, and refer to the Goddard declaration submitted under 37 C.F.R. 1.132 on 14 November 2004 as supporting the assertion that the gene is a useful marker for diagnosis of lung or colon cancer. This has been fully considered but is not found to be persuasive as it is off-point. Specifically, the claims are directed to PRO213-1 *polypeptides*, not PRO213-1 *genes*.

Appellant asserts page 11 of the Brief that pooled DNA samples from blood of healthy subjects is a proper control for gene amplification assays. Appellant's argument

has been fully considered, but is not persuasive. If genomic DNA levels didn't differ from tissue to tissue, then how can a particular DNA be diagnostic for a disease state? Since DNA can be amplified for a number of different reasons (including based on tissue damage from smoking or drinking), then the appropriate control would be the levels of the DNA in normal, healthy tissue rather than blood, absent evidence to the contrary. Additionally, the controls used in Pennica et al. (page 14718, column 1, last full paragraph) were matched tissue samples and Konopka used B-lymphoid cells because this was the sample being tested, contrary to Appellant's assertions. However, even if the prior art uses normal leukocyte DNA as a control in the gene amplification assay, it still does not establish that genomic DNA levels are predictive of protein expression levels and therefore, the data from Example114 cannot be extrapolated to protein expression levels and the protein still lacks utility.

Appellant argues (pages 12-13 of the Brief) that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes for from chromosomal aneuploidy. Appellant's argument has been fully considered, but is not found persuasive. In lung, the art shows that both cancerous and noncancerous lung tissue can be aneuploidy (see Sen et al. and Hittelman et al.). Also, in contrast to the art (*e.g.*, see Pennica et al., Konopka et al.), matched tissue samples were not used for controls in determining gene copy number in the instant application. Rather, the control DNA appears to have been isolated from blood. Given these details, one skilled in the art would conclude that data were preliminary. Even though it is desirable to identify individuals at risk for

cancer, the claimed invention cannot be used for that purpose. Because it is the PRO213-1 polypeptide and not the gene which is claimed, even if the reported amplification of the nucleic acid of SEQ ID NO:506 were due to aneuploidy, this does not support a diagnostic utility for the encoded polypeptide or antibody for the reasons previously discussed. The data pertaining to gene amplification do not convey utility to the claimed polypeptides, since amplification in genomic DNA as shown in the art fails to correlate with a corresponding increase in mRNA or polypeptide levels in many cases (see Pennica et al., Konopka et al., Godbout et al. and Li et al.).

Appellant asserts that based on the Ashkenazi Declaration (filed 10/04/04), gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. The Declaration of Dr. Ashkenazi explains that even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment, in that if the gene product is over-expressed in some tumor types but not others, this would enable more accurate tumor classification and hence better determination of suitable therapy, and additionally, if a gene is amplified by the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product. The Ashkenazi declaration filed under 37 CFR 1.132 on 04 October 2004 is insufficient to overcome the rejection of the claims based upon lack of utility because: it has not been demonstrated that the protein of the instant invention is differentially expressed in different tumors. If it was, the protein

would have a specific and substantial utility for tumor classification, but the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and is an invitation to experiment. The argument that if a gene is amplified but the gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target the gene product is also insufficient to overcome the rejection of the claims. If a specific gene product was known to be involved in cancer and if there were known compounds that could be used to target the gene product, this would be an acceptable utility. However, the gene product of the instant invention has not been demonstrated to be involved in cancer. Over-expression of a gene product in a cancer cell does not necessarily mean that the gene product is involved in the cancer and that targeting the gene product would be therapeutic. Additionally, there are no known compounds that would target the gene product. Finally, the Ashkenazi declaration supports the Examiner's position in that it provides further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels.

At page 13 of the Brief, Appellant argues that the Examiner is applying an improper legal standard when making the rejection and that the evidentiary standard to be used is a preponderance of the totality of the evidence under consideration. Appellant then asserts that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Appellant's argument has been fully considered, but is not found persuasive. Appellant's assessment of the question to be asked is on point and correct. However, a

review of the totality of the evidence under consideration must result in the conclusion that one skilled in the art would reasonably doubt the existence of a positive correlation between protein expression and gene copy number. Appellant again asserts that Orntoft, Hyman and Pollack collectively teach that gene amplification increases mRNA expression. However, the teachings of these references have been addressed and they do not demonstrate that there is a general correlation between gene amplification and mRNA expression, contrary to Appellant's assertion. The instant specification only discloses gene amplification data for PRO213-1 and does not disclose any information regarding PRO213-1 mRNA levels and there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues.

At page 14 of the Brief, Appellant addresses the Declarations of Dr. Polakis (filed 10/04/04 and 07/07/06) which assert that there is a correlation between mRNA levels and polypeptide levels. However, this Declaration filed under 37 CFR 1.132 is insufficient to overcome the rejection of the claims based upon 35 USC 101 and 112, first paragraph, because this correlation does not have bearing on the issue at hand, which is the lack of correlation between genomic DNA levels and protein levels. Appellant also refers to the Declaration of Dr. Scott which is directed to the sale of gene expression chips to measure mRNA levels. However, this Declaration filed under 37 CFR 1.132 is insufficient to overcome the rejection of the claims based upon 35 USC 101 and 112, first paragraph. First, evidence of commercial success, while probative as a secondary consideration of non-obviousness, has no bearing on the legal issue of

utility and enablement. Second, gene chips speak to the issue of whether mRNA levels are predicative of polypeptide levels, which is not relevant to the instant rejections. Appellant's statement that "the research community believes that the information obtained from these chips is useful" is misleading. It is not know for what purpose the researchers purchased these gene chips, but sale of a product is not evidence of patentable utility (e.g. the pet rock) nor does it establish a correlation between genomic DNA amplification and protein overexpression.

Appellant asserts at pages 14-15 of the Brief that the phrase "immediate benefit to the public" does not necessarily have to mean the invention is "currently available" to the public in order to satisfy utility requirements. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (MPEP 2170.01). The argument has been fully considered but is not persuasive. MPEP 2170.01 also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101". Even if the encoding polynucleotide has utility, this alone cannot support a utility for the encoded protein because the prior art provides sufficient support to make a correlation between genomic DNA and encoded protein level unpredictable.

At page 15 of the Brief, Appellant asserts that no further research would be necessary to determine how to use the claimed PRO213-1 polypeptides because if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. Appellant's argument has been fully considered, but is not persuasive because

there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues.

At page of the Brief, Appellant argues that it is more likely than not that if a gene is amplified in cancer, the encoded polypeptide is also expressed at an elevated level. This has been fully considered, but is not found to be persuasive. The relevant references have been addressed fully on the record, including in the instant Examiner's answer and the totality of the evidence under consideration does not lead to the conclusion that a correlation between gene levels and protein expression is more likely than not to exist, contrary to Appellant's assertions.

At pages 16-17 of the Brief, Appellant characterizes Pennica et al. as being limited to WISP genes and not speaking to the correlation of gene amplification and mRNA or protein expression for genes in general. At page 17 of the Brief, Appellant characterizes Konopka et al. as being limited to the *abl* gene, and not speaking to genes in general. Appellant does not need absolute certainty for an asserted use, but only that it is more likely than not that the product has that use. Appellant states at page 16, "The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that is it more likely than not, in general, that such a correlation does not exist." These arguments have been fully considered but are not found to be persuasive. Both Pennica et al. and Konopka et al. are relevant even though they are not reviews of gene amplification for genes in general, because they show a lack of correlation between gene amplification and gene product overexpression

for particular genes. The instant case also concerns a single gene. Pennica et al. showed that 2/3 WISP gene levels did not correlate with mRNA levels. Konopka et al. showed that protein levels for the *abl* gene were due to variation in mRNA levels not gene amplification. Moreover, the rejection is based on more evidence than just Pennica et al. and Konopka et al. (see, for example, Godbout et al. and Li et al, discussed below). The evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), and (2) no evidence has been brought forth regarding levels of PRO213-1 mRNA or polypeptide levels in cancerous tissue. Finally, Pennica et al. provide evidence that closely related WISP genes show unpredictable gene amplification, mRNA and polypeptide levels. As discussed in the rejections above, these references are pertinent to the lack of reasonable expectation that for any given gene the level of gene copy number will correlate with protein expression.

Appellant notes the citation of Godbout et al. and asserts that they have made of record three more recent references which were published in 2002 (Orntoft et al., Hyman et al., and Pollack et al.) which collectively teach that in general, gene amplification increases mRNA expression. Appellant's argument has been fully considered, but is not found persuasive. It is noted that the instant application claims priority to 1998, and thus the Godbout et al. reference, which was published in 1998, is reflective of the state of the art. Also, the publications from 2002 are not reflective of the state of the art at the time of the invention, which was sometime before 1998.

At page 18 of the Brief, Appellant asserts that Orntoft et al., Hyman et al., and

Pollack et al. collectively teach that in general, gene amplification increases mRNA expression. Appellant's argument has been fully considered, but is not persuasive. Orntoft et al. used the CGH method to look at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. However, Orntoft et al. do not look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time but rather, Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins. (See abstract.). The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO213-1 in the instant specification. That is, it is not clear whether or not PRO213-1 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, Orntoft et al. does not support utility and enablement of the claimed polypeptides. Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO213-1 would be correlated with elevated levels of mRNA, much less polypeptide. Since

Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification *fails* to correlate with increased mRNA/polypeptide levels. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung and colon cancer.

Appellant argues (page 18) Godbout shows a “good correlation” between protein levels and genomic DNA amplification. The argument has been fully considered, but is not persuasive. Appellant has missed the point of Godbout et al., which is that only those genes which confer a selective advantage to cell survival, for example a RNA helicase (though there are many other types of genes which could confer a selective advantage), would reasonably be expected to be amplified and have a correlative increase in encoded protein. The Examiner cannot find any reason to suspect that the protein encoded by the PRO213-1 gene would confer any selective advantage on a cell expressing it. On page 21167, right column, first full paragraph, Godbout et al. state, "It is generally accepted that co-amplified genes are not overexpressed unless they provide a selective growth advantage to the cell (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-

amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." There is no evidence in the instant application that PRO213-1 confers any growth advantage to a cell, and thus it cannot be presumed that the mRNA or protein is overexpressed even if the genomic DNA is amplified. Godbout et al. support the unpredictability that for any particular amplified genomic DNA, the corresponding mRNA or protein will be overexpressed.

Appellant also asserts that selective advantage to cell survival is not the only mechanism by which genes impact cancer and that mechanistic data is not a requirement for utility. Appellant also argues that Orntoft et al., Hyman et al. and Pollack et al. teach that gene amplification is a useful way to identify novel proteins not previously known to be associated with cancer. Appellant's arguments have been fully considered, but are not found persuasive because Orntoft et al., Hyman et al. and Pollack et al. are directed to gene amplification, mRNA levels, or polypeptide levels in lung and colon cancer. Furthermore, these cited references do not establish that amplification of genomic DNA results in protein overexpression, therefore, these references are not persuasive for overcoming the rejection of the instant claims.

Appellant argues (pages 18-19) that “Li et al. acknowledge their results differed from those of Hyman et al. and Pollack et al. (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression”, with Li et al. noting the difference may be from different methods used to study breast cancer and lung adenocarcinoma. Li et al. used a lower fold amplification threshold

(1.40 compared to 2.0 in the instant application). The argument has been fully considered, but is not persuasive. Even if Li et al. used a lower amplification threshold, it was shown that a *significant majority* of genes that are amplified do not have overexpressed mRNA (p. 2633, col. 2, end of first paragraph):

> In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but lack biological relevance in terms of the development of lung adenocarcinoma.

Similarly, Hyman et al. found less than half (44%) of *highly* amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Like Hyman et al., Pollack et al. concentrated on large chromosome regions showing *high* amplification (p. 12965). Pollack et al. also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability for any particular gene. PRO213-1 gene has not been asserted to be amplified in breast tumors. Both Li et al. and Hyman et al. show that less than half of the genes showing amplified DNA also showed elevated expression of mRNA. These references in combination with other references such as Godbout et al., Pennica et al. and Konopka et al. support a conclusion that one of skill in the art would not reasonably expect that for any particular amplified gene the corresponding mRNA or protein will more likely than not also be overexpressed.

At page 20 of the Brief, Appellant asserts that Example 114 of the specification

discloses that amplification is associated with overexpression of the gene product. Appellant's argument has been fully considered but is not persuasive because no data has been shown that would demonstrate such and association and because the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Pennica et al., Godbout et al., Hyman et al., and Li et al.

Appellant argues at page 20 of the Brief that the articles of Orntoft. et al., Hyman et al. and Pollack et al. teach that in general, gene amplification increases mRNA expression. Appellant further argues that over a hundred references, along with Declarations of Dr. Polakis and Dr. Scott have been submitted that in general, there is a correlation between mRNA levels and polypeptide levels.

These arguments have been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Appellant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which

overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner asserts that 2% does not provide a reasonable expectation that the slight amplification of PRO213-1 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

Appellant also refers to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed July 7, 2006. Appellant previously characterized the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Appellant previously concluded that all of the submitted evidence supports Appellant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the

expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO213-1 (i.e., data regarding amplification of PRO213-1 genomic DNA), and does not disclose any information regarding PRO213-1 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

Appellant also refers to a Declaration by Dr. Scott, however, this Declaration under 37 CFR 1.132 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action(s) because the declaration focuses on the question of whether or not mRNA levels are predictive of protein levels. Since the Scott declaration does not address the question

of whether or not amplified genomic DNA is predictive of increased polypeptide levels, it is not considered pertinent to the rejection.

Appellant refers to a decision by the Board of Patent Appeals and Interferences (Appeal No. 2006-1469). This decision is noted, but is not relevant to the facts of the instant application with regard to PRO213-1 because the evidence that is being relied upon relates to gene amplification and not mRNA levels from a microarray and Appellant has *not* established a showing that it is more likely than not that gene amplification correlates with increased protein levels. Accordingly, the Examiner maintains the conclusion that it is more likely than not that the PRO213-1 protein would *not* be expected to be overexpressed, and thus has no readily available utility as a cancer diagnostic. Appellant states at page 21 of the Brief that the Examiner has not presented any evidence specific to the PRO213-1 polypeptide to refute Appellant's assertion of a correlation between mRNA levels and protein expression. Appellant's argument has been fully considered, but is not persuasive. The issue in the instant application is that genomic DNA amplification is not predictive of increased polypeptide levels. Additionally, Appellant has offered no evidence specific to the PRO213-1 polypeptide to refute the Examiner's position.

At pages 21-22 of the Brief, Appellant continues to argue the Orntoft et al. reference. Orntoft et al. has been fully addressed in the arguments presented above. Furthermore, the Orntoft article was published in 2002, which is after the filing date of the instant application. Utility is determined as of the filing date *(In re Brana*, 51 F.3d at 1567), therefore, Orntoft et al. is not considered the state of the art for the instant

invention.

At pages 22-23 of the Brief, Appellant continues to argue the Hyman et al. reference. Hyman et al. has been fully addressed in the arguments presented above. Furthermore, the Hyman article was also published in 2002, which is after the filing date of the instant application. Utility is determined as of the filing date *(In re Brana*, 51 F.3d at 1567), therefore, Orntoft et al. is not considered the state of the art for the instant invention.

At pages 23-24 of the Brief, Appellant asserts that the Declaration of Dr. Polakis was presented to support the position that there is a correlation between mRNA levels and polypeptide levels, and that this would corroborate their asserts of utility of the claimed invention. However, Dr. Polakis does not establish that such data would have been known or would have reflected the knowledge of persons of ordinary skill on or before the application filing date, and utility is determined as of the filing date. Appellant asserts that the utility standard is not absolute certainty, and all that is needed is to show that it is more likely than not that an mRNA/protein correlation exists in order to meet the utility standard. Appellant's argument has been fully considered, but is not found persuasive. The Examiner has relied upon evidence which establishes that DNA amplification does not always affect the levels of a DNA's encoded product. There is no evidence in the instant specification that the levels of PRO213-1 mRNA or polypeptide in the tumor samples in which the PRO213-1 DNA had been amplified were also amplified. Therefore, a person of ordinary skill in the art would have reasonably doubted that PRO213-1 DNA amplification would affect PRO213-1 polypeptide levels

and therefore, would have reasonably doubted that the claimed PRO213-1 polypeptide would be a marker for cancer. With regard to Appellants assertion of "more likely than not", the results for different cancers using different DNAs show that sometimes DNA amplification results in a change in polypeptide levels, but sometimes it does not. For example, Godbout shows that out of 6 genes examined in the amplified 12Q13-14 chromosomal region, three were "rarely" overexpressed. There is no evidence in the record about the particular PRO213-1 DNA and what about it would have lead persons of ordinary skill in the art to expect its amplification would result in increased levels of the PRO213-1 polypeptide. Additionally, assuming that an event is “more likely” when it occurs more than 50% of the time, Appellant has not presented sufficient evidence that DNA amplification was known to alter polypeptide levels more than 50% of the time as of the effective application filing date.

At page 25 of the Brief, Appellant asserts that a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial and credible utility based on the Declaration of Dr. Ashkenazi (submitted 10/04/04). Appellant's argument has been fully considered but is not considered persuasive. While it may be true that lack of overexpression of a gene product may also provide useful information in tumor categorization, the specification does not disclose such further testing of PRO213-1 gene product expression levels to facilitate categorization. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products based on the claimed invention are not in “currently available” form. Furthermore, the specification provides no assertion that the claimed PRO213-1 polypeptides are useful

in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO213-1. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial. Finally, contrary to Appellant's assertions, Hanna et al. supports the rejection in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level of polypeptide expression must be tested empirically. Hanna et al. say these tests are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (col. 2, third full paragraph). The protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that "In general, FISH [gene] and IHC[protein] results correlate well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." This teaches away from using gene amplification in cancer diagnosis or treatment. The identification of subsets of tumors without correlation affirms the unpredictability of the findings. Therefore, the issues of HER-2 cannot be generalized to any gene expressed in a tumor. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments to reasonably confirm the real world context of the asserted utility. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Again, because Hanna et al. studied breast cancer, the warning by

Pollack et al. relating to the disparity in correlation of gene amplification and expression in breast compared to colon tumors is significant.

Appellant argues that Hanna and Mornin support the assertion that PRO213-1 is a tumor associated gene and that PRO213-1 is similar to the HER-2/neu gene disclosed in Hanna et al. Appellant's assertion has been fully considered but is not found persuasive. There is no evidence of record to suggest that PRO213-1 has any resemblance to HER-2/neu, which is a transmembrane glycoprotein with homology to the EGF receptor. High levels of expression of HER-2/neu are associated with rapid tumor growth, however, there is no evidence of record to suggest that high levels of expression of PRO213-1 have any effect on tumor growth. The level of HER-2/neu gene amplification has been correlated to recurrence risk in women wherein low-amplified tumors have a 54.5% recurrence risk compared to 85.7% for high-amplified tumors. There is no evidence of record that would suggest that PRO213-1 has a low-amplification versus high-amplification property and that this is correlated to any diagnostic measure. Furthermore, Hanna et al. disclose that subsets of tumors were found in which protein overexpression occurred without gene amplification as well as a lack of protein overexpression with gene amplification. In the instant application, there is no evidence of record which demonstrates any protein expression, so no conclusions regarding protein expression can be ascertained because protein expression is unpredictable and cannot be determined by merely measuring gene amplification as evidenced by Hanna et al.

At pages 26-27 of the Brief, Appellant concludes by arguing that, based on the asserted utility for PRO213-1 in lung or colon cancer diagnosis, the reduction to practice of the protein of SEQ ID NO:506 (Appellant mistakenly indicated SEQ ID NO:18), the disclosure of protocols for making chimeric PRO polypeptides such as those claimed and for recombinant expression of PRO213-1, and the gene amplification assay in Example 114, the skilled artisan would know exactly how to make and use the claimed polypeptide for diagnosis of lung or colon cancers. Appellant urges that testing would have been routine and not undue. This has been fully considered but is not found to be persuasive. The rejection is supported by the preponderance of the evidence. Regarding the gene amplification assay itself, it is noted that the assay did not correct for aneuploidy, which is a common feature of noncancerous, damaged lung epithelium (evidenced by Sen et al.). The specification does not assert a utility for PRO213-1 as a biomarker for damaged, precancerous tissue, and such is not a well-established utility. Gene amplification publications used matched tissue controls, unlike Appellant (Pennica et al., Godbout et al., Li et al.). Contrary to Appellant's assertions, the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Konopka et al., Pennica et al., Godbout et al., and Li et al. The declaration setting forth the expert opinion of Dr. Ashkenazi contradicts the assertion of utility in the specification, wherein the specification indicates that gene amplification is associated with protein overexpression but Dr. Ashkenazi indicates that this is not always the case. Hanna and Mornin provide evidence that the level of polypeptide expression must be tested empirically to determine whether or not

the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO213-1 was tested in normal and cancerous tissue, and thus the skilled artisan must perform additional experiments, as directed by the art. Since significant further research would have been required of the skilled artisan to reasonably confirm the PRO213-1 polypeptide is overexpressed in any cancer to the extent that it could be used as cancer diagnostic agent, the asserted utility is not substantial. Even more research would be required of the skilled artisan to determine if the claimed PRO213-1 polypeptides could be used as a cancer therapeutic, since there is no evidence that PRO213-1 plays a role in cancer formation or progression such that inhibiting PRO213-1 would result in effective cancer therapy. In the absence of information regarding whether or not PRO213-1 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO213-1 polypeptides as diagnostic markers and/or therapeutic target is simply a starting point for further research and investigation into potential practical uses of the claimed polypeptides.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

**(12) Oral Hearing**

It does not appear that Appellants have requested an oral hearing at this time. However, it an oral hearing is requested, the Examiner requests the opportunity to present arguments at the hearing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Christine J Saoud/

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